Long-term Effects of Exposure to Diethylstilbestrol

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In 1985 nearly 1,700 persons who had exposure to diethylstilbestrol (DES)—520 mothers, 1,079 daughters, and 94 sons—responded to a mailed questionnaire about their general health status. Results were compared with responses to the 1985 National Health Interview Survey and other population-based studies. As with research findings in animals, conditions that suggest possibly impaired immune function—that is, respiratory tract infections, asthma, arthritis, and lupus—were reported more frequently among the persons with DES exposure. Conditions that may involve altered endocrine function were also more frequent among such persons. Given the biased sample, findings from this preliminary survey are seen as guidelines to areas meriting more rigorous research.

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Between 1940 and 1972, a synthetic nonsteroidal estrogen, diethylstilbestrol (DES), was prescribed to millions of pregnant women throughout the United States and other countries in an attempt to treat or prevent pregnancy problems.[1] The failure of DES to improve pregnancy outcome was shown in the early 1950s[2]; the prescribing of DES during pregnancy, however, continued as a standard practice in the US, with about 3 to 6 million women and their offspring having exposure to the synthetic estrogen (an estimate based on figures from the Boston Collaborative Drug Surveillance program and the National Cancer Institute's Request for Proposal to establish the National Cooperative Diethylstilbestrol-Adenosis Project [DESAD], December 1, 1973).[3] Twenty years later, the first major unintended result of this therapy became apparent when a rare vaginal tumor in young women—clear cell adenocarcinoma—was linked to prenatal DES exposure.[4] At that time, the Food and Drug Administration withdrew approval for the use of DES as a miscarriage preventive.

The identification of the extremely rare vaginal and then cervical cancer marked the first known instance of human transplacental carcinogenesis. While the clear cell cancer risk is low for daughters with exposure to DES—about 1 in 1,000 by her mid-30s[5]—a large, well-controlled study has shown a twofold increase in the risk for cervical and vaginal dysplasia and carcinoma in situ among these women.[6]

Research on humans has concentrated on genital tract pathologic disorders. Among daughters with exposure to DES, non-neoplastic changes and reproductive problems are more common than cancer.[7-12] Less research has focused on sons with the exposure, and results have been more contradictory. Studies, however, have shown increased rates of urogenital tract abnormalities—including epididymal cysts and undescended testes—in men with prenatal exposure to DES.[11,13]

Questions remain about additional health effects associated with DES exposure, especially among those receiving exposure in utero. Clearly, prenatal exposure resulted in more than a single defect, including conditions that have a higher background rate in the general population than did the originally identified vaginal tumor. With the great majority of this cohort still younger than 40 years, the age of increased cancer risk for various sites has yet to be reached.

Research using experimental animal models and concerned primarily with elucidating mechanisms of DES effects raises questions regarding future health consequences in the human population. While these studies cannot directly predict human outcomes, they suggest possible areas of inquiry. A critical question requiring study in humans is whether prenatal DES exposure results in long-term immunologic effects. In mice, perinatal DES exposure in certain genetic strains results in impaired immune system functioning.[14,15] Corresponding immunologic consequences in humans could be important not only for the development of cancer but for a range of other health conditions. Other areas of concern arising from experimental studies in animals include the breast and ovary in daughters,[16-20] the prostate and testes in sons,[21] and endocrine alterations in both women and men with prenatal exposure to DES.[16,22,23] Concerns about possible health effects beyond genital tract disorders prompted a survey of the health status of persons with known exposure to DES. The aim of this preliminary survey was to provide guidelines regarding areas meriting more rigorous research.

Methods

In 1985 a questionnaire was mailed to 2,000 persons who subscribe to a quarterly newsletter published by DES Action, USA. This voluntary, nonprofit organization provides information and support to those with DES exposure and their health care providers. The questionnaire was also sent to 3,000 persons who had contacted the organization for infor-

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ABBREVIATIONS USED IN TEXT
DES = diethylstilbestrol
MCA = 3-methylcholanthrene

mation such as physician referrals but who had not subscribed to the newsletter.

About 1,700 persons responded—520 mothers, 1,079 daughters, and 94 sons. Between 80% and 90% reported definite exposure. Approximately 40% of the mothers and daughters and 20% of the sons reported that they had received validation of their exposure—more than 50% of those requesting such information. Exposures were reported between 1941 and the late 1970s, the latter in Mexico.

Where possible, the rates of conditions reported were compared with those reported in the 1985 National Health Interview Survey[24] or in population-based studies.[25,26]

Results

Many conditions already known or suspected to be associated with DES exposure were reported more frequently than expected. For example, 1.3% of the daughters reported clear cell adenocarcinoma of the vagina or cervix compared with less than 0.1% in published reports.[5] This disparity is presumably due to self-selection of the sample. That is, daughters who have experienced clear cell adenocarcinoma would be more likely to subscribe to the DES Action newsletter and therefore be overrepresented. Such a bias is less likely to occur in those contacting the organization for information only than in those subscribing to the newsletter because they may be less certain of exposure or have experienced less frequent or severe known DES effects. Analyses comparing the rates of DES-associated conditions among these two groups (not shown) indicate that the rates were higher among those subscribing to the newsletter, while rates among those contacting DES Action, USA for information only were similar to those in published reports based on unbiased samples of persons with DES exposure—that is, those identified by reviewing records.

Conditions not known to be associated with DES exposure were also reported more frequently than expected. As can be seen in Table 1, the number of reported colds, flu, and respiratory tract conditions during the past year in daughters and sons was three times as high as the number reported for comparable age and sex groups in the 1985 National Health Interview Survey.[24] Among mothers receiving DES, the number was about twice as high. Both surveys are based on self-reported health conditions.

TABLE 1.—*Respiratory Tract Conditions Among Adults From the Diethylstilbestrol (DES) Survey (This Study) and the National Health Interview Survey (1985)**

DES Survey			*National Health Interview Survey*		
Person	*Age, years*	*Rate†*	*Person*	*Age, years*	*Rate†*
Daughters, N=1,079	14-44	255	Women	18-44	96
Sons, N=94	14-44	207	Men	18-44	69
Mothers, N=520	27-77	130	Women	45+	59
				All ages	94

*From National Center for Health Statistics.[24]
†Number of respiratory tract conditions per 100 persons per year.

TABLE 2.—*Prevalence Rates (%) of Selected Conditions Among Adults With Diethylstilbestrol (DES) Exposure*

	DES-Exposed (This Study)			*Comparison**		
Condition	*Person (N=1,693)*	*%*	*No.†*	*Group, age*	*%*	*P Value‡*
Asthma						
	Daughters	9.6	104	Women, <45 years	4.2	≤.001
	Sons	14.9	14	Men, <45 years	3.6	≤.001
	Mothers	8.3	43	Women, 45-64 years	2.9	≤.001
Arthritis						
	Daughters	7.8	84	Women, <45 years	4.4	≤.001
	Sons	8.5	8	Men, <45 years	2.2	≤.001
	Mothers	41.9	218	Women, 45-64 years	32.5	≤.001
Lupus erythematosus						
	Daughters	0.7	8	Women, all ages	0.002	
	Sons	0.0	0	Men, all ages	0.0002	
	Mothers	1.0	5	Women, all ages	0.002	
Diabetes mellitus						
	Daughters	1.0	11	Women, <45 years	0.7	≤.05
	Sons	3.2	3	Men, <45 years	0.6	≤.01
	Mothers	5.6	29	Women, 45-64 years	5.1	NS
Prostate problems						
	Sons	14.9	14	Men, <45 years	0.3	≤.001

NS=not significant

*All data are from the National Center for Health Statistics,[24] except the data for lupus erythematosus, which are from Isselbacher et al.[25]
†Daughters numbered 1,079, sons numbered 94, and mothers numbered 520.
‡Based on χ^2 statistic.

Other conditions reported in apparently high numbers when compared with population-based data[24,25] are presented in Table 2. Prevalence rates were higher among those with exposure to DES for asthma, arthritis, lupus, diabetes mellitus, and prostate problems. Virtually all of these differences were statistically significant (based on χ^2 statistics). Arthritis reported by daughters and sons generally occurred early: the median age for the beginning of arthritis was 24 years for daughters and 17 years for sons. In addition, 38 daughters (3.5%) reported high prolactin levels, and 7 (0.6%) reported pituitary tumors. The annual incidence rate of pituitary tumors in women 15 to 44 years old was reported to be 0.007 between 1970 and 1977 in Minnesota.[26]

While it was expected that conditions known to be associated with DES exposure would be overreported, conditions with no known association were considered unlikely to be overreported to the same degree. Rates of the conditions presented in Table 2 were compared for respondents who had subscribed to the DES Action newsletter and those who had contacted the organization for information only, on the theory that the latter group should exhibit less reporting bias. Unlike the rates of conditions known to be associated with DES exposure, there was generally no difference in the rates of these other disorders in the two groups. In addition, rates of asthma, arthritis, and respiratory tract problems were calculated for DES daughters who were both sure of their exposure and reported DES-associated conditions—adenosis, cervical anomalies such as hoods or ridges, or clear cell adenocarcinoma of the vagina or cervix. These women are more likely to have had early or higher dose exposures. Rates were comparable to those reported for DES daughters in Tables 1 and 2 and still significantly higher than those for similarly aged women from the National Health Interview Survey. This was the case whether or not the 12 daughters with cancer were included in the analyses.

Discussion

The present survey represents a preliminary look at possible health effects of prenatal exposure to DES in humans beyond those already known. As such, it should be considered as a guide to areas needing further investigation in less biased samples. The findings, however, are consistent with those of experimental studies in animals and indicate a need for follow-up in the human cohort. Of particular note are conditions that suggest impaired immune function, such as infectious illness, allergic and autoimmune conditions, and malignant tumors. Studies of certain genetic strains of mice with exposure to DES during the critical neonatal period of immune system ontogeny—analogous to the first trimester of human pregnancy—show persistent, lifelong immunosuppression. The main DES effect is a reduced number of T-helper cells, important for the induction and regulation of many immune responses.[14,15] B-cell response is impaired in assays requiring T-cell mediation but is normal if corrected for T-helper numbers.[14] Experiments with varying combinations of B and T cells in vitro show that the defect is in T-cell number but not function.[14]

Mice with neonatal exposure also have a reduced number of natural killer cells thought to recognize and kill certain tumor cells.[14,15] Following injection with a classic carcinogen (3-methylcholanthrene [MCA]), DES-exposed mice show a reduced ability to resist tumors; MCA-induced sarcomas appear in greater numbers and at a faster rate.

Our findings regarding asthma, arthritis, and lupus are also consistent with those of a small study of human peripheral blood lymphocytes suggesting a hyperreactive immune response in women with in utero exposure to DES.[27] Another small study of the daughters suggested possible functional alterations of natural killer cells.[28] Even more suggestive, our findings are consistent with those of a recent preliminary report from the largest ongoing follow-up of DES daughters, the federally funded Diethylstilbestrol Adenosis Project.[29] This report indicates about a twofold increase in autoimmune conditions in women with prenatal exposure compared with controls.[29] One small study of daughters who had had DES-associated cancer or reproductive problems showed no consistent increase in the rates of infectious disease but a suggestive increase in the rates of autoimmune disease compared with controls.[30]

Evaluating immunologic consequences in women and men with DES exposure will be complicated by possible genetic contributions and by varying dosage and timing of the prenatal exposure. Furthermore, health consequences might become detectable only as the population ages, when the immune system generally declines in competence.

Possible pathologic disorders of the prostate, as noted in our survey, were also noted in experimental models of DES effects in rodents.[21] In preliminary studies of mice with neonatal DES exposure, evidence of cytologic malignancy in the area of the prostate appeared only in the experimentally treated animals.[31] Recent experiments in which human fetal prostate tissue was grafted into DES-treated and untreated athymic nude mice and then allowed to continue growing revealed ductal dilation and persistent distortion of ductal architecture; these conditions could contribute to early or increased development of prostatic neoplasms (S. Mee, G.R. Cunha, C.V. Yonemura, et al, "The Effects of Diethylstilbestrol on Human Prostate Development," unpublished data, 1987).

Further inquiry should also focus on a possible increased prevalence of elevated prolactin levels among DES daughters. Substantial endocrine alterations occur in rodents; more specifically, experimental studies show that perinatal DES exposure results in a disruption of hypothalamic-pituitary feedback systems, including the regulation and production of prolactin.[16,22,23] While endocrine effects of a similar magnitude are not apparent within the human cohort, there could be an increase of more subtle functional alterations in daughters or sons (or both) with exposure to DES. Although difficult to measure, abnormal endocrine function could be contributing to a diminished reproductive capacity in ways beyond the more apparent and well-documented structural anomalies. Two small studies of plasma hormones in the daughters suggest abnormalities that may reflect a disturbance of hypothalamic-pituitary-ovarian function.[32,33] An additional study suggests that hyperprolactinemia may be a significant factor in infertility in daughters with DES exposure.[34]

Comprehensive follow-up of DES-exposed daughters and sons is required to answer questions about the long-term consequences of prenatal exposure. As the cohort ages and reaches new "milestones" of increased health risks, such follow-up can contribute to a more adequate assessment of this population's risks and to the early detection of various health conditions that may be affected by prenatal DES exposure and be responsive to treatment. In addition, an increased

knowledge of the health consequences associated with DES exposure addresses a broader scientific need to examine fully the results of this reproductive exposure. Women and men with in utero exposure to DES constitute a unique, identified cohort from which much can be learned about the hormonal effects on both normal and abnormal human development. This cohort can provide a greater understanding of developmental biology, sex differentiation, and pathologic processes in humans. Beyond the basic knowledge to be gained are implications for therapeutic substances in use currently or considered for the future.

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